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THE TOXICITY OF PYROLYSIS PRODUCTS FROM A CHLOROTRIFLUOROETHYLENE-ETHYLENE COPOLYMER (HALAR RESIN)

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13. ABSTRACT

This report was presented at the Proceedings of the 2nd Annual Conference on Environmental Toxicology, sponsored by the SysteMed Corporation and held in Fairborn, Ohio on 31 August, 1 and 2 September 1971. Major technical areas discussed included toxicological evaluation of volatile halogenated compounds, protection of the public against air pollution and toxicological problems with aircraft, missiles, and space vehicles.

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PAPER NO. 14

THE TOXICITY OF PYROLYSIS PRODUCTS FROM A CHLOROTRIFLUOROETHYLENE-ETHYLENE COPOLYMER (HALAR RESIN)

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INTRODUCTION

Halar*, a new copolymer of chlorotrifluoroethylene (CTFE) and ethylene having a 50/50 mole ratio and a high degree of one-to-one alternation, offers an attractive combination of properties including excellent chemical resistance, nonignitability, good electrical properties, and a good balance of mechanical properties. Variations in molecular weight, additives, and cross linking give slightly different characteristics to the copolymer (poly CTFE-E). The thermoplastic resin can be extruded, injection molded, or powder coated. Poly CTFE-E is thus suitable for a wide variety of applications.

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Mention of commercial products or concerns does not constitute endorsement by the U. S. Public Health Service.

The structure elucidation of poly CTFE-E was reported by Sibilia et al. (1971) and is also described in this paper. The products formed when poly CTFE-E undergoes thermal decomposition and the acute toxic action in experimental rats following the inhalation of those pyrolysis products have been studied at the National Institute for Occupational Safety and Health in cooperation with the Plastics Division of the Allied Chemical Corporation, Morristown, New Jersey.

STRUCTURE ELUCIDATION

The structures of CTFE-E copolymers have been shown by nuclear magnetic resonance and infrared measurements to contain a high percentage of one-to-one alternating units (Sibilia et al., 1971).

The nuclear magnetic resonance spectra of CTFE-E copolymers (figure 1) show five distinct bands which are assigned to methylene protons in different structural environments. Band assignments were made by analysis of the spectra of a series of ethylene-chlorotrifluoroethylene polymers of different comonomer content. The upfield peak (1.3 ppm) in the nuclear magnetic resonance spectra is assigned to methylene protons in ethylene sequences and the downfield peak (2.6 ppm) to methylene protons in CTFE-E-CTFE sequences. The peaks centered at 1.8 and 2.3 ppm are assigned to methylene protons in E-E-CTFE sequences. The mole fraction of one-to-one alternating units in poly CTFE-E may be calculated from the relative area of the peak at 2.6 ppm and the total ethylene content. The degree of alternation in commercial Halar resin averages 82%. Ethylene content as measured by elemental analysis averages 49%.

Precise measurements of the chlorotrifluoroethylene and ethylene sequence distribution in Halar were obtained from infrared spectra. Infrared spectra of a series of poly CTFE-E copolymers varying in ethylene composition from 80 to 50 mole percent are shown in figure 2. Analysis of these spectra showed that the bands at 1471 cm^{-1}, 1450 cm^{-1}, 1435 cm^{-1}, 1398 cm^{-1}, and 1385 cm^{-1} are associated with vibrations of methylene groups in different structural environments. The absorbance at 1471 cm^{-1} is sensitive to ethylene block content, and that at 1450 cm^{-1} is sensitive to alternating structure.

Mole fractions of various sequences in the copolymer were calculated from infrared measurements. Typical commercial Halar resin contains 82% alternating structure, 8% ethylene blocks, and 10% chlorotrifluoroethylene blocks.

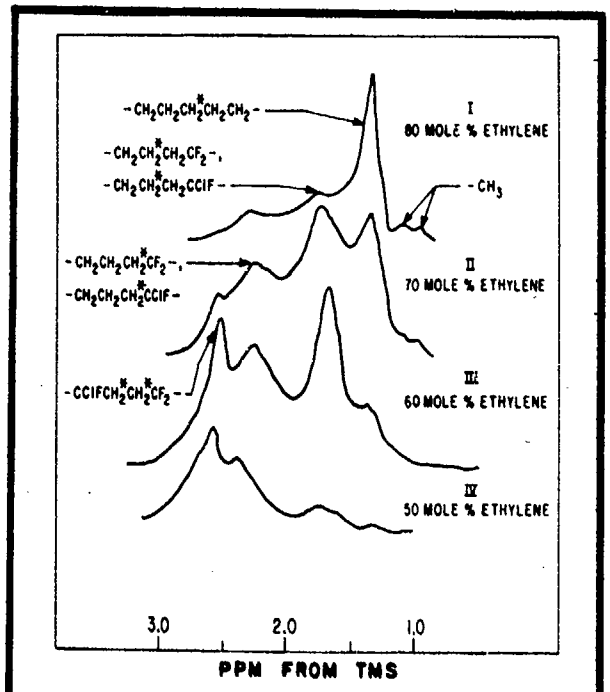

FIGURE 1. NUCLEAR MAGNETIC RESONANCE SPECTRA OF CTFE-E COPOLYMERS.

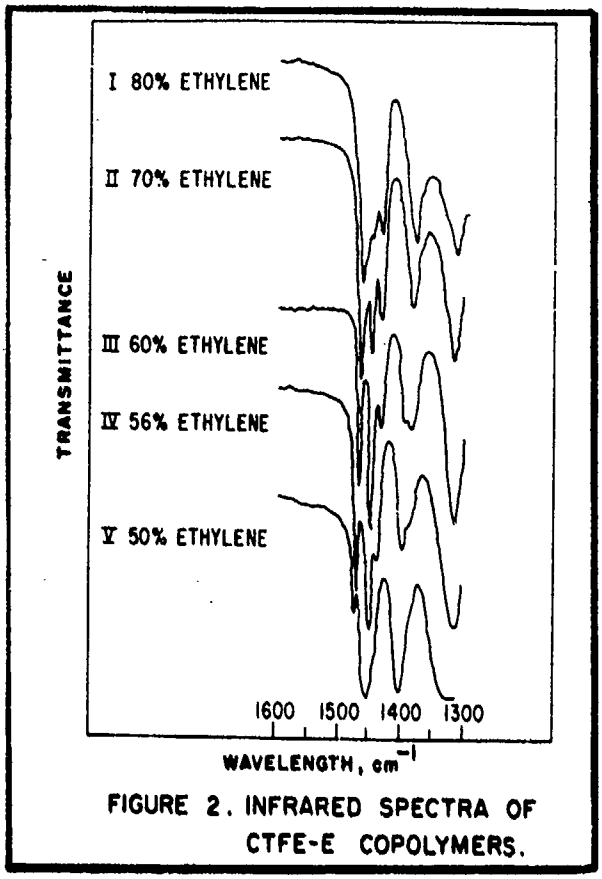

FIGURE 2. INFRARED SPECTRA OF CTFE-E COPOLYMERS.

PHYSICAL PROPERTIES

Poly CTFE-E exhibits certain extraordinary physical properties which make this copolymer potentially useful in various commercial applications.

The resin is insoluble in all common solvents below 140 C and is resistant to oxidation by concentrated nitric acid and 50% chromic acid at temperatures up to 100 C. No solvent has been found which will stress crack the resin.

Poly CTFE-E has been rated as either nonflammable or self-extinguishing in various flammability tests. When placed in a flame, the copolymer chars but does not melt or drip. On removal from the flame, poly CTFE-E immediately extinguishes and exhibits no afterburn. Its oxygen index is 64, and its UL verticle rating is SE-O.

In comparison to available fluorocarbon polymers, poly CTFE-E has a good balance of mechanical properties (table I). Its tensile strength is significantly higher than the prefluorinated polymers, polytetrafluoroethylene (PTFE) and fluorinated ethylene-propylene (FEP), and approximates that of polyvinylidene fluoride (PVF_2). Its flex modulus is nearly as high as that of PVF_2, and its impact strength is equal to or greater than that of FEP, depending upon the temperature at which the measurements are made.

As also shown in table I, poly CTFE-E is an excellent electrical insulation material. The dielectric strength is greater than 2000 V/mil in 10 mil thicknesses. Its dielectric constant is low and unaffected by temperature up to 200 C. The dissipation factor varies between 0.0005 and 0.015 depending on frequency and temperature. The electrical properties of poly CTFE-E are superior to those of PVF_2 and approaches those of PTFE and FEP.

The resin is melt processable and can be extruded, injection molded, and powder coated. It melts at 265 C and has good processing characteristics in the temperature range of 245-290 C. Suggested uses for the copolymer include wire and cable insulation, coatings, molded parts, tubing and film.

TABLE I

PROPERTIES OF POLY CTFE-E AND OTHER FLUOROCARBON POLYMERS

PROPERTIES	POLY CTFE-E	PTFE	FEP	PVF_2
MELTING POINT, °C	241.0	327.0	285.0	171.0
SPECIFIC GRAVITY	1.69	2.18	2.15	1.77
OXYGEN INDEX	64.0	100.0	100.0	43.0
TENSILE STRENGTH, psi	6000-8000	3000-4000	2000-3000	5000-7000
YIELD STRENGTH, psi	5000	3000	2000	6800
ELONGATION AT BREAK, %	200-250	250-350	250-350	50-200
FLEX MODULUS, psi	240,000	95,000	85,000	280,000
DROP WEIGHT IMPACT AT 23 °C, lbs	160	160	160	160
DROP WEIGHT IMPACT AT 80 °C, lbs	160	---	30	10
DIELECTRIC CONSTANT AT 60 Hz	2.5	2.1	2.1	8.0
DISSIPATION FACTOR AT 60 Hz	<0.0005	<0.0002	<0.0003	<0.018
VOLUME RESISTIVITY, ohm/cm³	$>10^{16}$	$>10^{18}$	$>10^{18}$	$>2\times10^{14}$

IDENTIFICATION OF PYROLYSIS PRODUCTS

The pyrolysis products of five poly CTFE-E samples having different properties were investigated using thermogravimetric (TGA) and mass spectrometric techniques supplemented by chemical analyses. The samples studied are described as: (1) low molecular weight copolymer, (2) high molecular weight copolymer, (3) high molecular weight copolymer cross-linked by electron-beam irradiation, (4) high molecular weight copolymer, which contained 0.25% CaO as a filler, cross-linked by electron-beam irradiation, and (5) high molecular weight copolymer, which contained 0.25% CaO as a filler, cross-linked by irradiation with cobalt-60.

Thermograms of the samples were obtained using a du Pont 600 TGA instrument programmed for a temperature increase of 15 C/min with an air flow of 40 cc/min. The thermogram of the electron-beam irradiated CTFE-E sample, which is typical of those obtained for all five copolymers, shows that this material decomposes in two major steps, the first taking place in the temperature range of 350 C to 450 C and the second occurring at temperatures greater than 450 C (figure 3).

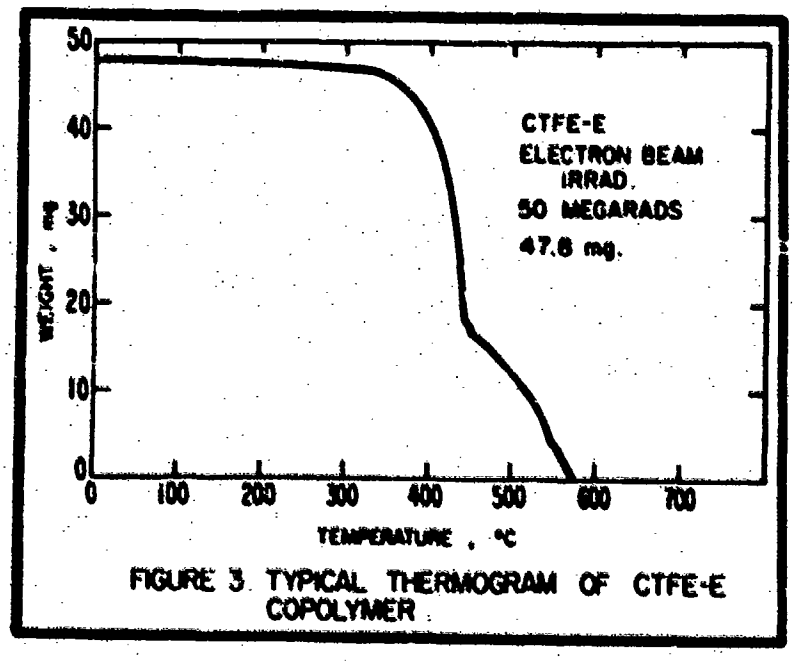

FIGURE 3. TYPICAL THERMOGRAM OF CTFE-E COPOLYMER

The effluent gases from the TGA furnace were passed through appropriate solutions and assayed for hydrolyzable fluoride and chloride with specific ion electrodes. These gases were also analyzed for carbon dioxide and carbon monoxide with Kitagawa detector tubes. Formaldehyde was indicated as a pyrolysis product by its characteristic odor and was confirmed by reaction with a chromotropic acid-sulfuric acid solution as described in P. H. S. No. 999-AP-11 (1965).

Fluoride and chloride ions and carbon dioxide were found only during the first stage of decomposition, whereas carbon monoxide was detected as a pryolysis product in both temperature ranges.

Pyrolysis products of the CTFE-E copolymers were examined with a Bendix Time-of-Flight mass spectrometer, Model 12-107. These products were formed by introducing pellets of the plastic material into a platinum-lined Monel tube heated by a small electric furnace as described previously by Kupel and Scheel (1968). The decompositions were carried out in an air atmosphere under a controlled air flow of 22 cc/min and at a temperature of 600 C. The products of decomposition were passed into the ion source of the mass spectrometer. The ions shown in table II were found in the mass spectra of pyrolysis products originating from all poly CTFE-E samples. Mass 20 was attributed to hydrogen fluoride, and mass 36 was ascribed to hydrogen chloride. These compounds accounted for nearly all the hydrolyzable fluoride and chloride found in the effluent gases from the TGA furnace. A small amount of carbonyl fluoride, indicated by its major peak at mass 47, also made a slight contribution to the hydrolyzable fluoride content. Mass 44 confirmed the results of detector tubes that carbon dioxide was a major pyrolysis product. Carbon monoxide was identified by the comparison of the measured 14 to 28 mass peak ratio with that of nitrogen.

TABLE II

MASS SPECTRUM OF PYROLYSIS PRODUCTS OF POLY CTFE-E

MASS NO.	ION	MASS NO.	ION
19	F^+	51	CF_2H^+
20	HF^+	63	$C_2F_2H^+$
28	CO^+	64	$C_2F_2H_2^+$
31	CF^+	65	$C_2F_2H_3^+$
35	$^{35}Cl^+$	69	CF_3^+
36	$H^{35}Cl^+$	75	$C_3F_2H^+$
37	$^{37}Cl^+$	77	$C_3F_2H_3^+$
38	$H^{37}Cl^+$	81	$C_2F_3^+$
44	CO_2^+	85	CF_2Cl^+
47	COF^+	95	$C_2F_3H_2^+$

TOXICITY STUDIES

A toxicity study of pyrolyzed low and high molecular weight poly CTFE-E was conducted in a manner similar to that described in previous publications on the pyrolysis of polytetrafluoroethylene by Coleman et al. (1968) and Scheel et al. (1968) and of chlorotrifluoroethylene by Birnbaum et al. (1968).

A quarter-inch rod of poly CTFE-E was fed into a $1\frac{1}{2}$-inch Monel pipe heated with an electric furnace at 550 C to provide continuous pyrolysis of the polymer. The pyrolysis products were passed into an animal exposure chamber.

Male Carworth strain rats, weighing 220-250 grams each, were used in the exposure studies. All individual exposure groups consisted of 10 animals. In each exposure, two rats were first placed in each of five cages which were attached to a chamber airlock door. After the chamber had achieved an equilibrium concentration of poly CTFE-E pyrolysis products the airlock door was rotated to position the caged animals in the chamber atmosphere. After a two-hour exposure the animals were removed from the chamber and immediately returned to their housing cages.

During the exposures the chamber atmospheres were assayed for hydrolyzable fluoride, hydrolyzable chloride, formaldehyde, and carbon monoxide. Samples of the atmosphere to be analyzed for hydrolyzable fluoride and chloride were collected with a midget impinger containing 10 ml of a solution that was 0.05 M in sodium acetate, 1.0 M in potassium nitrate, and adjusted to pH 5 with acetic acid. The sampling, which was conducted at a rate of 1.13 liters per minute, was continued for 15 to 30 minutes. The solutions were then analyzed with specific ion electrodes. The chamber atmospheres were also sampled for formaldehyde with midget impingers containing a 1% sodium bisulfite solution for 45 minutes at a rate of 1.13 liters per minute. These solutions were analyzed for formaldehyde by the ACGIH Bisulfite Method (American Conference of Governmental Industrial Hygienists, 1958). The carbon monoxide concentrations, measured with an MSA portable carbon monoxide detector, were in the range of 225-400 ppm.

As shown in table III, appreciable hydrolyzable fluoride concentrations, expressed as hydrogen fluoride, were found in the chamber atmospheres along with lesser quantities of hydrolyzable chloride, expressed as hydrogen chloride and traces of formaldehyde.

The mortality data given in table III show a direct correlation with the level of hydrogen fluoride found in the exposure chamber. By plotting the mortality probit against the hydrogen fluoride concentration according to the method of Miller and Tainter (1944), the LC_{50} for hydrogen fluoride is shown to be about 42.5 ppm (figure 4). This level of hydrogen fluoride was attained by the thermal decomposition in air of approximately 18 grams of the copolymer per hour and the introduction of the resulting pyrolysis products into the chamber in an airstream of 40 liters per minute.

TABLE III

TOXIC PRODUCTS OF CTFE-E COPOLYMER PYROLYSIS

g/hr	HF, ppm	HCl, ppm	HCHO, ppm	Mortality
15.79	19	8	0.6	1/10
17.48	48	15	—	6/10
12.72	52	11	0.4	7/10
17.85	73	47	0.6	10/10
19.20[a]	33	19	0.7	3/10
19.46[a]	23	12	0.3	2/10

[a] HIGH MOLECULAR WEIGHT CTFE-E COPOLYMER.

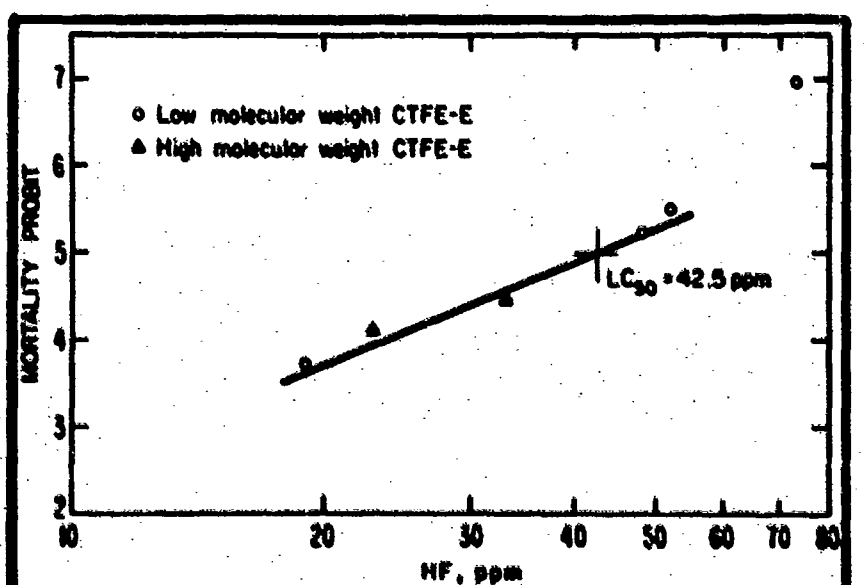

FIGURE 4. LC_{50} CTFE-E PYROLYSIS PRODUCTS

PATHOLOGY

Four rats that died during or immediately after a two-hour exposure to poly CTFE-E pyrolysis products were necropsied within 30 minutes of death. Gross inspection of the lungs showed areas of hemorrhage. The cut surfaces of the lungs were edematous, and a frothy fluid could be expressed from the tracheae. The hearts, livers, and kidneys appeared normal. Microscopic examinations were made of hematoxylin-eosin stained sections of pulmonary lobes, tracheae, livers, and kidneys. The lungs exhibited diffuse capillary hemorrhage, engorgement of perivascular lymphatics, and disruption of alveolar septa. Sloughing of respiratory epithelia occurred in the tracheae and bronchi. The livers showed vascular congestion and early vacuolation of hepatic cells. In the kidneys, moderate tubular necrosis was observed, and a pink-stained proteinaceous material was present in the tubular lumens.

SUMMARY

Thermal decomposition of a one-to-one alternating copolymer of chlorotrifluoroethylene and ethylene (poly CTFE-E), produced commercially as Halar, begins at 350 C and is complete at 600 C. The principal gaseous products formed by pyrolysis of poly CTFE-E at 600 C in air have been identified as hydrogen fluoride, carbon dioxide, carbon monoxide, hydrogen chloride and formaldehyde. Acute toxic inhalation studies using experimental rats have been conducted on the pyrolysis products formed at 550 C in air. A correlation of exposed animal fatalities could be made only with the hydrogen fluoride concentration in the exposure chamber. The LC_{50} for hydrogen fluoride was determined to be about 42.5 ppm for a single two-hour exposure. The toxic effects on the exposed animals were characterized by primary irritation of the respiratory tract and pulmonary edema and hemorrhage.

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OPEN FORUM

MAJOR CARTER (NASA, Manned Spacecraft Center): This question is directed to both Doctors Weinstein and Bullock. I'd like to hear both of them comment on it. Would either one of you care to comment on the possible differences in free radical formation between carbon tetrachloride and the dichloromethane, and how it possibly relates to differences you have presented today, both biochemically and pathologically?

DR. BULLOCK (Arthur D. Little, Inc.): On that point, I wonder if you were listening when I was giving my views to someone during coffee break. I would be pleased to expand on that. I think that as far as carbon tetrachloride is concerned there is some very good evidence that free radicals are indeed involved in the hepatotoxicity of carbon tetrachloride. I think that is as far as published literature goes but I think that one can speculate further, and I would be pleased to do so, with the aid of the blackboard and some simple textbook diagrams. If we're talking about the formation of radicals from carbon tetrachloride in liver, we presumably are talking about CCl_4 going to a trichloromethyl radical plus a chlorine radical. If we're talking about the same kind of transformation with things like dichloromethane or chloroform, we ought to be talking about CH_2Cl_2 to Cl_2CH plus a chlorine radical, and for chloroform we ought to be talking about $HCCl_3$ going to $HCCl_2$ plus a chlorine radical. We ought to be able to correlate the relative toxicities with the ease of formation of these radicals, and in simple textbook terms, the ease of formation of radicals can be described as breaking the carbon-chlorine bond. This goes in two steps, the first of which is associated with a stretching - it is a simple transition state theory in the terms of a chemist to this (blackboard illustration). And, if we plot the energetics involved for this transformation, on this ordinate reaction coordinate (again simple physical chemical textbook term) and energy. The energy course for this transformation is from starting material through the transition state which is energy rich and the bond breaking comes down to products. The rate is determined by the so-called free energy of activation and goes in a way proportional to or equal to an expression of this sort where we have a preexponential factor to the $e^{-\Delta F}$ where ΔF is the free energy of formation. Now, these rates, therefore, should vary with the free energy of activation for the bond breakage which in turn should vary with the thermodynamic properties of these bonds; that is, it would be nice if in this picture you anticipate a correlation between relative toxicity of these three chlorocarbons and the ease of formation of radicals, which in turn is proportional to or related to the bond energy of the carbon-chlorine bond for the rate of formation, and these numbers are measurable free energy of activation, you ought to be able to get from this so-called appearance potential for ions, which a mass spectroscopist has, and this is what one would predict from some simple arguments, that the toxicity should be correlated with these energies. I am not aware that anyone has looked at this problem in these terms, but I think it would perhaps be interesting to do so.

DR. PARKER (NASA, Ames Research Center): If you assume that this ΔF has about one-third the energy required, let's say from the heats of formation, you'd say this is between 35 and 40 kcal per mole. I'm just curious as to where that energy is going to come from. I can see that certainly in a normal situation for photochemical induced reactions which you have set up here, where you pump 50 to 60 kcal per mole into a bond, as a chemist I am not familiar with the biological source of that much energy to accommodate that; it has to site fit; it has to do all the good things; and I don't see how that would happen with classes.

DR. BULLOCK: I can't answer that question in detail, but I will say that it is known to happen. These chlorocarbons are metabolized by liver microsomes.

DR. PARKER: But not necessarily by a free radical mechanism.

DR. BULLOCK: No, not necessarily by a free radical mechanism.

DR. PARKER: I think that because you can write, sir, a free radical process for these does not in any sense mean that these systems would necessarily proceed by a radical mechanism in a biological system. That's the only point I want to make.

DR. BULLOCK: But a bond cleavage process, whatever you might postulate, should be correlated with an energetic diagram of that sort in some way, so if you don't say radicals, it will be some chemical transformation correlatable in those terms, terms like that.

DR. PARKER: There seems to be a lot of interest at this conference on the role of free radicals at surfaces, and I was wondering if anyone has planned or can carry out Electron Spin Resonance (ESR) type of experiments where you basically could allow the enzyme or whatever to come in contact with this and then follow the appearance of the ESR signal with the unpairing that would be associated?

DR. BULLOCK: I think you might have difficulty in finding it.

DR. PARKER: Because of the speed of the reactions?

DR. BULLOCK: No, not at all. The microsomes themselves give an ESR signal; there is copper in there which gives you an ESR signal and also the iron in the porphyrins of the cytochromes appears to be high spin and does give a signal. It might be interesting, however, to watch changes in that signal during the course of these.

DR. PARKER: You would think if this were going on okay one step further, it's possible that these compounds that you've postulated, the radical intermediates, would quench those spins by recombination reactions with them, because there would be available pairs of free electrons. I'm willing to bet that where these compounds would reside as a result of being formed, if you could give me enough energy, they would be sitting on those unbonded sites, and you might see a depression in the ESR signal.

DR. BULLOCK: That is possible. You incidentally do see a depression of the ESR signal when we put in things like aniline. The signal shifts and they are changed. Aniline, of course, is not a radical by itself. Whether or not you would see evidence for radical intermediates, you might see a change in the presence of carbon tetrachloride, just because it goes into the lipid-rich membrane and sits there, resulting perhaps in conformational changes which in turn manifest themselves in changes of the ESR signal for the iron porphyrin.

DR. PARKER: I prefer to believe that the way these compounds work is by tripping the phospholipid arrangements that exist in the membrane cells rather than a specific chemistry.

DR. BULLOCK: May I clarify one thing? This is an expansion on a theory expressed at great length in Pharmacological Reviews (1967) for mechanisms of toxicity of carbon tetrachloride. I do not want to be put in the place of assuming this theory is correct, but I merely wish to expand on the implications of that general theory for the other chlorocarbons.

DR. SCHEEL (U. S. Public Health Service): My only comment is that I don't think we should at the moment, from the evidence we have now, base our conclusions on tentative hypotheses. I think that what we need is to take a look at the hydrolysis reactions and the basic ion formation reactions because there are real good pieces of evidence that would indicate that in the body mechanism you don't necessarily have to add the activation energy all in one piece - you can add it in several pieces, and that this is why mechanism discussion at this stage may be a little bit premature. It is good to have a hypothesis, but it argues ad infinitum.

MR. DARMER (SysteMed Corporation): I have a couple of questions to ask of Dr. Scheel, relating to the mortality data which you described. What was the species?

DR. SCHEEL: The rat.

MR. DARMER: How were these exposures accomplished?

DR. SCHEEL: By inhalation exposure.

MR. DARMER: Inhalation in a chamber?

DR. SCHEEL: Yes.

MR. DARMER: And, for what length of time were these?

DR. SCHEEL: This was a two-hour exposure.

MR. DARMER: The LC_{50} value which you showed on your slides was for the combination of all gas-off products?

DR. SCHEEL: That is right.

MR. DARMER: What was the approximate temperature of this gas?

DR. SCHEEL: The temperature at which we pyrolyzed it was 550 C in the furnace.

MR. DARMER: Was this cooled in any fashion?

DR. SCHEEL: It was cooled before going into the chamber, in a dilution air stream.

DR. HODGE (University of California Medical Center): I'd like to follow this up. Aren't those values rather low to get such high kills?

DR. SCHEEL: You mean in terms of quantity?

DR. HODGE: Yes, the total ppm of HF, HCl, and formaldehyde, and what else, wasn't mentioned.

DR. SCHEEL: In the work at Rochester that was done on a four-hour exposure, the LC_{50} was about 33 ppm, and so this is about in line with what we would expect from fluoride exposure. Now the pathology is a typical fluoride picture of lung edema and kidney nephritis with protein going into the tubules. So it looks to me like on a gross basis at the moment that we're talking about fluoride toxicity primarily.

MR. WANDS (National Academy of Sciences): I have two or three very short questions I'd like to ask. First of all, Dr. Scheel, were there any particulates such as you have seen in some of your other plastic pyrolysis studies?

DR. SCHEEL: Yes, in this kind of pyrolysis the generation of particulates is always there because the breakdown products rearrange and this takes a matter of a few minutes in terms of the rearrangement and they are still rearranging in the chamber. The density of particulates in this particular case is less than we had with Teflon. The particulate generation in this pyrolysis was smaller than in the case of Teflon.

MR. WANDS: Dr. Bullock, were your exposures of 1000 ppm for 30, 60, and 90 days continuous or five hours a day, something like that?

DR. BULLOCK: These exposures were continuous. These were the exposures carried out here at Wright-Patterson Air Force Base.

MR. WANDS: Dr. Weinstein, you used the Thomas domes for these exposures. Were they at altitude or at ambient atmospheric pressure?

MAJOR WEINSTEIN (Aerospace Medical Research Laboratory): Ambient atmospheric pressure.

DR. THOMAS (Aerospace Medical Research Laboratory): The reason for this was saving money. Oxygen costs quite a bit.

MAJOR VAN STEE (Aerospace Medical Research Laboratory): I would like to present some observations to supplement those provided by Dr. Bullock in his paper. If one accepts the proposition that the availability of cytochrome P-450 in some way limits the rate of metabolic degradation of hexobarbital, our observations of the effect of exposure of mice to dichloromethane on hexobarbital sleeping time are consistent with the changes in P-450 seen by Dr. Bullock. Our methods for the determination of the duration of hexobarbital sleeping times in this experiment were identical to those described earlier in this conference for our work with fluorocarbons. The results are illustrated in figure 1. Exposure to 5000 ppm CH_2Cl_2 for 30 days significantly prolonged the duration of hexobarbital sleeping times. Exposure to 1000 ppm for 30 days significantly prolonged sleeping time but these values were significantly lower than those obtained from the animals exposed to 5000 ppm. The sleeping times in the group exposed to 1000 ppm remained prolonged throughout the 90 day exposure and no significant differences were observed among the samples obtained from the dome at 30, 60, and 90 days.

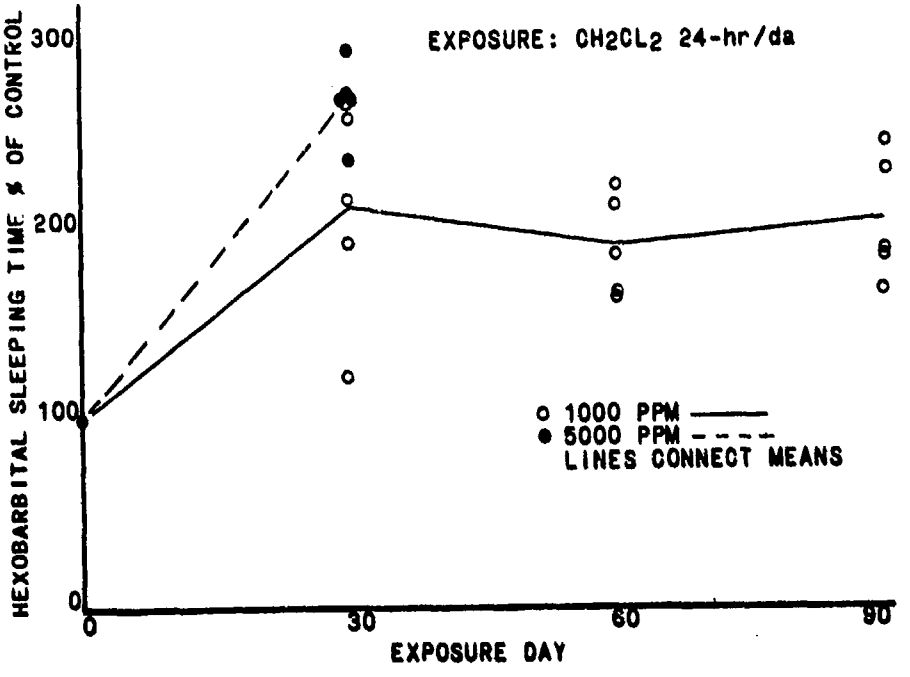

Figure 1.

DR. PARKER: I have a couple of comments I'd like to make. I'm sorry I didn't get in on the early part of Dr. Scheel's talk. Did you notice any difference in the mass spectroscopic distribution of products depending upon the size of the sample when you carried this experiment out, if you did your pyrolysis in oxygen? Was this geometry-dependent?

DR. SCHEEL: The mass spectrometry system is a small furnace system where we can either bring it up slowly or we can preset the temperature and dump it in rapidly.

DR. PARKER: These were done in air?

DR. SCHEEL: These that I have shown here were done in air. Now, we used oxygen atmospheres at a temperature around 450, and we were looking for an increase in carbonyl fluoride but it didn't happen. It still dehalogenates even in an oxygen-rich atmosphere. Now, if you do a nitrogen decomposition, the dehalogenation reaction still goes on and you get the breakdown products, but the carbon monoxide, etc. doesn't appear and you get what is essentially left in the furnace - a char of just plain carbon.

DR. PARKER: The reason I brought it up is this. These fluorocarbons can decompose and do decompose by chain scission or they decompose by scissioning processes, and when they do, they form a boundary layer which surrounds the polymer with monomer. Now, this is very true in the case of Teflon. We carry out the experiment by using a flat plate of polymer, heated from below with a stream of gas passing above the polymer. We begin to observe reactions only in the gas phase at temperatures of around 300 C, where that unzipping monomer in equilibrium is at the surface, and is being attacked by the gas phase. It's my contention that a polymer that produces any one of these monomeric or rearrangement products does not allow the oxygen to come in contact with the polymer and it forms a transpiring sheath around the polymer. And so if you have a polymer which is very stable to oxygen, and very stable to unzipping, what happens is that you get up to a very high temperature, as in the case of Teflon, the reaction is between the monomer and the gas, and not the polymer. I think the same things apply here; for example, you can form an awful lot of carbonyl fluoride from Teflon at 300 C, but you don't see this because it rearranges itself into CF_4. But, if you admit moisture to the system, just a slight amount, you capture the COF_2 as it comes off the surface. The second point about your heat treating - do you believe that your heat treating induces instabilities in your polymer system; that is to say, cage free radical sites which then tend to make the polymer unzip the hydrohalogenate or suffer internal chain reactions more readily than if you had not heat-treated it?

DR. SCHEEL: The heat treating process as far as I can explain it would be simply a disproportionation reaction in which some hydrochloric acid cracks out.

DR. PARKER: But this would have to come from a fluorine cleavage which would form a free radical which would then find another free radical.

DR. SCHEEL: Well, you go ahead and talk free radical. I talk chemistry.

DR. PARKER: Well, that is the way it was reported in the Journal of Polymers since 1962. This is an important point.

DR. SCHEEL: I think I would disagree with your premise that you have to have a monomer to get COF_2.

DR. PARKER: No, I didn't say you have to have, but what I'm simply saying is that direct action of the oxygen on a polymer backbone, that is giving off gas fraction, prevents the oxygen from getting at the surface, almost completely.

DR. SCHEEL: I think that I would totally disagree with this on the basis of the work on Teflon that we did, because here you're getting a recombination of oxygen-containing fragments to form a particle which has totally different properties than Teflon.

DR. PARKER: I don't agree with your publication necessarily. Basically, how come when we heat the Teflon specimen from below, and we collect with a mass spectrometric probe right at the top of the specimen, the gases that come off - we see COF_2, we see HF and we recover the Teflon polymer that is the residual polymer on the plate unchanged?

DR. SCHEEL: What you're seeing in a thermal degradation, which is what you're doing, is carbon to carbon fragmentation as a result of thermal degradation, and you're measuring what is happening in the gas phase reactions as a result of the introduction of double bonds in a carbon-carbon fluorine molecule, and you're getting the ethylene reactivity which is very, very high. You've changed your reactivity from the single bond carbon chain reactivity to a carbon-carbon double bond reactivity.

DR. PARKER: I agree. I don't think you can attack a chain of Teflon oxidatively.

DR. ROBERTSON (Allied Chemical Corporation): I would like to respond and make a point which seems to be lost here somehow. Perhaps you're familiar with the concept of ceiling temperature in polymer science. That is the temperature above which the equilibrium between monomer and polymer shifts back to monomer, and above the ceiling temperature you cannot polymerize the material, or if you heat a material above the ceiling temperature, it will depolymerize. In the case of TFE, this apparently happens; it depolymerizes, generating monomer. This is not the case with Halar. It dehydrohalogenates and leaves an almost graphite-like residue. It does not degrade back to monomer, to any significant extent.

DR. PARKER: Just for the record, just how much of char residue does one get with the decomposition of the polymer?

DR. ROBERTSON: You lose about 64 percent of the weight when you burn it, and if you were to calculate the total content of halogen, it would be very close to that.

DR. SCHEEL: Take a look at our charred samples up here. This is a real good illustration in terms of the way in which this thing goes at different temperatures.

FROM THE FLOOR: How, Dr. Scheel, does the toxicity of TFE compare with Halar?

DR. SCHEEL: Basically I think it compares about one-third in terms of quantity; in terms of speed of reaction, it is a little faster simply because the fluoride is there as the reactive component and you don't have to wait for the carbonyl fluoride to hydrolyze. The carbonyl fluoride is almost exclusively a deep lung irritant, it doesn't irritate the upper respiratory tract appreciably at all. This is just simply a manifestation that the hydrolysis reaction is so slow that it is inhaled and in the deep lung before it begins to hydrolyze, and so, the upper respiratory irritation doesn't appear. In the case of a mixture of hydrochloric and hydrofluoric acid, we're talking about hydrochloric acid as a very severe upper respiratory irritant. It is so severe that I don't think anyone could ever stay in an atmosphere where this stuff was coming apart; it is very irritating, and so we get both upper respiratory and lower respiratory irritation here.

DR. HODGE: I take it, Dr. Scheel, that you are comparing the toxicity of the pyrolysis products at comparable levels of temperatures?

DR. SCHEEL: Yes, fairly comparable because the Teflon breakdown was done at 525° and the breakdown here was at 550°, so we're talking about the same general temperatures. We had to continue for two hours in order to kill anything, whereas the Teflon data was for one-hour exposures, so when I say that this was about half as toxic or less than half as toxic, this is based upon a time-weighted judgment, rather than any hard and fast data.

DR. ROBERTSON: I'd like to make one other point. In fires where escape is possible, a person might breathe carbonyl fluoride because it is not a potent irritant, but it is a potent toxicant. He would be more likely to hold his breath if he were in a room filled with HCl and perhaps wouldn't die if he could escape.

DR. PARKER: I'd like to comment on this relative toxicity. I mean it is a little confusing because you have time and you have temperature. We continually seek a means of comparing the relative toxicity of one polymer versus another. There is a treatment by Heicklen and Epstein which is very interesting and I offer it to the audience for what it is worth. What they basically do is a thermogravimetric analysis of a polymer and from that they numerically deduce the rate constants for decomposition. They then isolate the compounds of the principal pyrolysis reactions which have

occurred. They determine by mass spectrometry the relative weight fraction of each of these components in the gas phase. Then they plot the log of the rate constant times the summation of the individual components in the gas phase divided by LC_{50} against 1/T, and it is remarkable for those of you who haven't seen this, that Teflon and others all fall on very straight lines. I think it's only one of the Vitons which comes along and makes a break and you know that if you compare, for example Fluoril, which you must have heard about in NASA, with Teflon, there are seven orders of magnitude of difference in the relative toxicity calculated and displayed relativistically in this way.

DR. HODGE: May I ask again the names of these two authors?

DR. PARKER: They are Heicklen and Epstein, and it is in an Aerospace Corporation report, and it goes back about two years. Now, many of my people regard this as a gem of an idea. Obviously there are synergistic effects which occur in here, and there are hydrolytic effects which occur, and there are oxygen reactions in the gas phase. This is the Aerospace Corporation report, done for the Air Force. I think there is a lot of refinement in this that has to come. It is not the absolute answer, but gives us one heck of a good handle, and it does permit the combination of temperature and time and reasonable kinetics.

DR. BACK (Aerospace Medical Research Laboratory): I caution you against putting too much credence in this particular document, because the basis upon which the toxicity was "guesstimated" put apples and pears in the same box, and you can't compare apples and pears. So, the straight lines extrapolated were figments of their imagination, I'm afraid. Although it is an Air Force publication, it shouldn't have been published.

DR. THOMAS: In other words, it is a lousy report.

DR. PARKER: Do you disagree with the principle?

DR. BACK: The principle is nice, but there are no data.

DR. PARKER: You're not arguing with my evaluation of the principle, you're arguing about your contractor's ability to perform the assigned research function.

DR. BACK: I'm arguing about the data that compare Viton, and the whole four or five other compounds. With the lack of data, they were comparing one-hour toxicities with four-hour toxicities, with two-week toxicities, with mice data, rat data, monkey data, and none of it correlated.

DR. PARKER: The equation as it is written only requires that you have a knowledge for the relative comparison of the LC_{50}, a knowledge of what the species are, what comes off each of the principal reactions, and the rate constants and their temperature dependence for each one of the reactions. I can't tell if they had good data or not because the report doesn't say, but I do think it is a gem of a very good idea in terms of ways, going back to the original question, of comparing time, temperature, compared with fundamental thermochemical processes which are releasing the toxins from the surface. Now, the fact that they didn't have good data, I apologize for.

DR. THOMAS: I would like to call your attention to a better publication and it is not specifically about these compounds, but it's been published by the National Academy of Sciences Committee on Toxicology, "Guidelines for Short-Term Exposure Limits." You're talking in this case about the short-term exposure, very brief, and it laid down the ground rules that you just don't take apples and oranges and you don't go through mathematical gyrations and predict toxicity. You have got to do the exposures.

DR. ROWE (Dow Chemical Corporation): I'd like to change the subject, if I may. I would like to address a question to Mr. Haun with regard to the methylene chloride exposures. One of the principal observations that was made was a tremendous change in weight. I was wondering what state of nutrition these animals were in and whether or not these animals were fed while in the chamber.

MR. HAUN (SysteMed Corporation): Food was available to them at all times.

DR. ROWE: That tells me also then that there could have been a considerable amount of absorption and adsorption of those high concentrations of material on the food, so there was a considerable amount of ingestion going along at the same time. At least I've seen this happen. And the other one is, were they eating? Were there records of food consumption so we have an idea of whether or not they were in a horrible state of inanition?

MR. HAUN: In answer to that, we didn't maintain absolute data on food consumptions, merely observations on our part. But, this was very noticeable and one didn't really have to measure it, particularly in the case of the large animals. They got so bad and in such poor condition they simply couldn't get to the food many times. There was definitely malnutrition operating here.

DR. ROWE: The question is one of separating out the effect of malnutrition from the effect of the compound.

DR. SCHEEL: I would like to make a comment with regard to the same point. In order to have inanition in a short-term experiment which lasts the length of time he talks about, I think we're going to have to have some kind of central nervous system blockage for appetite. This is very unusual in my judgment as to the behavior of the animals, because a dog when he is hungry will take your arm off.

MR. HAUN: In this case, as far as the dogs were concerned, particularly those exposed to the highest dose level of 5000 ppm, they couldn't take anybody's arm off; they were really in bad shape. Certainly, this is true a little later on when we had six of the eight dogs die in the 1000 ppm exposure level; they were in extremely bad shape there too. In regard to actual appetite suppression from the effects of this compound, I think certainly that was operable too, but we have no evidence to support that. It's my opinion in the case of the rats that the only real effect on the rats was an appetite suppression from the compound itself. Interestingly enough, from a curiosity point, I'm wondering why no rats died in this study. In retrospect, it would have been interesting to have done some metabolic studies on the rats. Apparently they are able to blow off this compound, one way or another, metabolize it or what have you, and get away with it, whereas the other species can't do this at all.

DR. ROWE: One other question. Did you do any analysis of the food to see how much methylene chloride may have been adsorbed and consumed orally?

MR. HAUN: I think that was done, but I'll have to call on some aid from somebody else. Dr. MacEwen can answer that, perhaps.

DR. MAC EWEN (SysteMed Corporation): I'd like to back up just a little bit on this whole question. The food consumption wasn't measured because these dogs are group-housed, that is four to a pen within the chamber itself, so that it's not feasible to measure each individual animal's food consumption. Secondly, the food was completely replaced each day. That means there is some adsorption during the day in a continuous exposure. We didn't measure this adsorption but we did remove the excess food. The animals did not stop eating completely; all the animals ate to a certain degree.

DR. ROWE: The principal reason for bringing up the subject was that in some experiments done several years ago, I ran into a similar situation of attempting to feed animals and expose them 24 hours a day to high concentrations of materials that were readily adsorbed on food. We found that by giving 23.5 hours of exposure and allowing the animals to perhaps ventilate a lot of the material absorbed (and I suspect this may happen because I don't know exactly the degradation curve, but I would expect it to be fast), they would eat very well, rapidly in a half hour, and have changed the pattern completely.

DR. MAC EWEN: These animals in these facilities when they are fed, if they're not in seminarcotic states, normally do that; they go right to the pan and the dog food pan is emptied within an hour or so after introduction of food on a daily basis. The equilibrium blood levels of methylene chloride measured in each of the domes would indicate an equilibrium that was uniform in both of them; it would not have been a five to one ratio if they had been getting a significant dose from their food intake of more methylene chloride. The muscle mass loss in these animals was greater than you would normally expect to see in simple starvation and the response was somewhat different than you would expect to see in starvation. Does that clarify it a little bit?

DR. LEE (Environmental Protection Agency): I have a question for Dr. Bullock. I think I noticed considerable differences among the control groups in that experiment. Would you elaborate on that?

DR. BULLOCK: I can't, other than to say it is generally known that levels of the cytochromes b and b_5 will change somewhat with age; this is well known for rats. I don't know the situation for mice; it is not impossible that these variations in control level are due to the fact that after 90 days these animals obviously are 90 days older than the first group. Other than that, I cannot offer an explanation.

DR. LEE: In conjunction with your cytochrome electron transport system, have you looked at the mitochondrial electron transport system?

DR. BULLOCK: We did no work with mitochondria.

DR. CAMPBELL (Environmental Protection Agency): I wonder if you would elaborate, Dr. Thomas, on your recommendation for the continuous exposure versus, let's say, interrupted exposures to help compress the toxic potential of your experiment, and in particular what effect brief interruptions such as an hour might have for servicing animals, and gassing off through exhalation, and so on, in relation to 24 hours as is possible in your Thomas domes.

DR. THOMAS: I'll take your last question first. Theoretically, there must be a concentration during continuous exposure to a toxic chemical where the intake and excretion is in a perfect balance and that compound can be handled without any physiological injury. Let us assume 500 ppm of something, okay? Continuously for 24 hours, all right? If you have to open up the chamber and interrupt the exposure, that value might look more than 600 ppm. We are playing here with the idea of a summation of interest type of damage in chronic toxicity, and Dr. Harris and Dr. Back and I have been toying for a long time with the idea of getting good biological, mathematical models established on continuous exposures. With a number of compounds which we have used, we have found that as the exposure progresses the organism tries harder and harder to cope with it. Now, as I mentioned before, we will have to set valid 1000-day limits one of these days. There is no way to do all the exposure work at three dose levels for 1000 days, so our ideas are not clear yet on this subject - how you can do a good biological mathematical model on this. But, by accelerating the chronic toxic effect with continuous exposure, I think we might put a handle on this. Does that answer it?

DR. CAMPBELL: Yes, very good for now. I am interested in this modeling of yours for similar reasons.

DR. THOMAS: Well, let's get together.

DR. CAMPBELL: Wonderful! The second point I have is a comment on your disappearance of the phasic activity which you assert may be due to the estrus cycle.

It has been my experience that when you depress activity, via some toxic or CNS suppressive manner, you also compress the range of variability, so that activity is disappearing in that way. Also suggested, of course, is the possibility that these things may be having an actual reproductive effect.

DR. THOMAS: We missed the boat by not doing vaginal smears, and we found it out too late.

DR. CAMPBELL: Of course, there are other studies, and laboratories have used reproductive effects as an index of toxicity and this might be included in some of your regimens.

DR. THOMAS: We will be looking into this thoroughly and we will be using injection techniques and go through "typical drugs," tranquilizers, hydrocarbons and everything else by injection rather than by inhalation techniques.

DR. PROCTOR (The Boeing Company): I'd like to suggest there may be some behavioral factors compounding the experiment when you use a half hour or hour cessation of exposure for feeding. For one thing, if animals have not been fed for 23 hours, there is a hunger factor and the act of feeding to stimulate continued feeding when food is made available to them. Another thing, and I suspect that most of these compounds they're being exposed to are objectionably odorous, especially in pyrolysis. If the upper respiratory tract has a chance to clear out these odors, the odor of feed can come through loud and strong for the stimulation of hunger. There can be a great many factors which can make a change in an experiment, and repercussions can often be very great, so that the difficulty of comparing experiments can be as complex as when we change exposure times.

DR. FRIESS (National Naval Medical Center): May I pursue just one notch further the point raised about 1000-day limits for spacecraft application? We are being driven rather mercilessly by NASA at this point to make some estimations of permissible limits for 1000-day application, and therefore the point finally settled on that you and we are thinking about the matter has to be pushed one more notch up the wall. I'd like to ask at this stage in history if you have a feel for what factor of compression in time, and therefore what factor elevation and concentration, one can now at this point design his experiments with animals to get the first approximation toward rough data so the engineers can proceed on design?

DR. THOMAS: Have you ever heard a loaded question like that?

DR. FRIESS: You brought it on yourself by raising the issue twice, and it is terribly important to us.

DR. THOMAS: I'll tell you one thing, it is very hard at this stage of the game to give an estimate, but you're giving at least 4.5 times the dose per day, so if we're lucky we can just reduce the actual exposure run to one-third of 1000 days. I think

that figure is within reach. What is not within reach is that it's very hard for all of us to get a program going in the biological modeling area, because most of this research is not sponsored by people who are interested in long-term effects. I have the same problem in the Air Force. This is systems related, and if the system is Skylab, funds are unavailable for anything longer than a Skylab mission.

DR. FRIESS: Can I push one more notch? You gave me a factor of three, and I'd like to see if I can push one more notch to a factor of five because this would permit us to have the same experimental models running for the 180-200 day exposures that we are going to talk about for 1000. Now, does your gut feeling say that the 1000-day is not going to be much different from the 180-day situation?

DR. THOMAS: Not at this stage! Without having a model and cranking in all these data, and you remember we must have been looking at 80 different compounds with continuous exposure in the past seven or eight years. But, you know somebody has to write a program first, you've got to test the case and feed in all the old data, and it is available, and only by experimenting with this program will you really find out whether it works or not. My nose tells me it will work, but I have no proof of this.

DR. FRIESS: Will the program give you an extrapolation factor of five, from 200 to 1000?

DR. BACK: Since we have to struggle with this together, I think there is one saving grace in most of the long-term experiments that we have been doing, and this seems to be the fact that for almost all of our long-term experiments the animals seem to come to equilibrium, and the variation around the mean gets smaller and smaller. The animals become more and more alike, and if we can use this as a first indication that long-term experiments of three years or more may not be necessary, maybe we're on the right track. In other words, if we can get through a year's experiment at a given level, I think our chances for extrapolating to three years are getting better and better, and the more work we do, the more it indicates that we are on the right track.

DR. FRIESS: Is there some stage in history that 350-day exposures might be the best practical solution at the moment for recommendations bearing on the total mission over the next 10 years?

DR. BACK: We are going to have to use six-month data because that's all there is, and at this moment in time we're going to have to guess with six-month data. It seems the longer the animals go the more they are able to compensate for whatever deficit they started out with, and they get better and better as they go along. We're going to have to work with the data right now.

DR. ROWE: I know what Dr. Friess is talking about, and I know what Dr. Thomas' problems are in getting this sort of system outlined. But remember that these people who are going to be in this situation are going to have uncontaminated food and they're

going to have an adequate amount of good water and this factor I feel is so important in evaluating these long-term studies that we do keep our animals in a state of proper water balance and food nutrition balance. And, that could complicate this whole business of extrapolation.